

To: Caryn Cohen, M.S.
Office of Science, Center for Tobacco Products
Food and Drug Administration

From: Professor Gregory N. Connolly
Director, Center for Global Tobacco Control
Harvard School of Public Health

Date: January 3, 2012

Re: Submission on Dissolvable Tobacco Products

We are submitting this testimony on dissolvable tobacco products in accordance with the Family Smoking Prevention and Tobacco Control Act (FSPTCA), Section 907 Tobacco Product Standards (a)(3)(B)(i) and (f) , which at the request of the Secretary requires the Tobacco Product Scientific Advisory Committee to issue a report and recommendations on dissolvables tobacco products..

According to this section, three considerations shall be considered in assessing the public health impact:

- Risks and benefits to population as a whole including users and non-users of dissolvable tobacco products;
- Increased or decreased likelihood that existing users will stop using such products;
- Increased or decreased likelihood that those who do not use tobacco products will start using such products.

Based on these criteria, our testimony will address these issues by examining the construction and constituents of dissolvable tobacco products, nature of the product, potential risks to public health, and potential effects on users and non-users. Our testimony will rely on an analysis of the product, constituents, patents, internal industry documents, as well as published and unpublished literature.

In addressing Section 907, we feel that research on smokeless products, and Swedish and American snus in particular, is a source of information given the similarities of the physical properties of the products and the marketing techniques of the tobacco industry and the absence of actual research on dissolvables. However, more research clearly needs to be done specifically on dissolvable products before they should be allowed for sale. We are only submitting this data to show the multiple adverse effects of Swedish Snus like products. Before the criteria outlined in section 907 are finalized, retail sales of dissolvable tobacco products should be suspended until comprehensive scientific analysis has been completed.

1. Definition of Dissolvable Tobacco Products:

Dissolvables are products which are intended to dissolve in the mouth without expectoration, and contain tobacco and numerous added constituents whose purpose is to deliver nicotine to the user via oral mucosal absorption. Recently, U.S. cigarette manufacturers, RJ Reynolds and Altria, have introduced dissolvable products into test markets using popular cigarette brand names – Camel, Marlboro and Skoal. Camel dissolvables, which exist in the form of orbs, strips, and sticks, are currently marketed in Colorado and North Carolina. In 2011, Altria introduced Marlboro Sticks and Skoal Sticks into test markets. Marlboro Sticks and Skoal Sticks consist of a slim wooden stick coated in finely milled tobacco and added constituents. These products may appear similar to Star Scientific dissolvable tobacco tablets, known as Ariva and Stonewall, which have been sold in the U.S. since 2002. However, a careful review of the appearance, patents, changes in portion size, free nicotine and harmful constituents and other identifying factors show the great likelihood numerous modifications to any predicate product sold as of 2/15/2007.



Figure 1: Dissolvables Packaging

2. Patents and Internal Industry Documents:

A review of U.S. patents for dissolvable products identified several different methods for constructing and manufacturing dissolvable tobacco. Among these methods are pasteurization, pH control, and moisture control. Patented compositions and processes for dissolvable tobacco include the combination of a tobacco component, binder, humectants and flavorants, as well as the addition of non-tobacco components to tobacco followed by compression. A review of the patent literature shows a striking understanding by the manufacturers of the role of added constituents in affecting interoceptive stimuli, in all likelihood enhancing abuse potential. The

FDA and TPSAC should require disclosure of all dissolvable patents and conduct a careful review of them.

3. Internal Tobacco Industry Document Research

Internal tobacco industry research revealed thousands of documents appearing on the topic of dissolvable tobacco marked as confidential for possible proprietary reasons. It is therefore unavailable to the public. Given the potential for these documents to enhance scientific understanding of dissolvable tobacco products, the FDA should require full disclosure of these documents and review these as confidential documents if the law applies, present their findings confidentially to the TPSAC and reclassify all non-confidential information and release to the public.

Table 1: US Patents for Dissolvable Tobacco

U.S. Patents for Dissolvable Tobacco				
Title	Date	Company	Author	U.S. Patent Number
Tobacco Compositions	11/3/2005	Clark Elbing LLP	Strickland	Provisional application No. 60/518,352
Tobacco Compositions	8/31/2006	Clark Elbing LLP	Strickland	US 2006/0191548 A1
Smokeless Tobacco Compostion	2/7/2008	RJ Reynolds	Dube	US 2008/0029110 A1
Chewing Article for Oral Tobacco Delivery	11/13/2008	Philip Morris	Gedevanishvili	US 2008/0276948 A1
Smokeless Tobacco Compostion	1/29/2009	RJ Reynolds	Brinkley	US 2009/0025739 A1
Smokeless Tobacco Compostion	1/29/2009	RJ Reynolds	Mua	US 2009/0025738 A1
Tobacco Compositions	5/28/2009	Fish Richardson PC	Strickland	US 2009/0133704 A1
Smokeless Tobacco Compostion	10/12/2010	RJ Reynolds	Dube	US 7,810,507 B2
Tobacco Articles and Methods	10/26/2010	US Smokeless Tobacco	Strickland	US 7,819,124 B2
Smokeless Dissolvable Compressed Tobacco Product	11/4/2010	Philip Morris	Bivehed	US 2010/0275936 A1
Smokeless Tobacco Compostion	3/17/2011	RJ Reynolds	Dube	US 2011/0061666 A1
Tobacco Articles and Methods	3/29/2011	US Smokeless Tobacco	Strickland	US 7,913,699 B2
Tobacco Articles and Methods	4/5/2011	US Smokeless Tobacco	Strickland	US 7,918,231 B2
Smokeless Tobacco Compostion	5/24/2011	RJ Reynolds	Brinkley	US 7,946,295
Dissolvable Tobacco Film Strips and Method of Making the Same	5/24/2011	Philip Morris	Wrenn	US 7,946,296

The FDA should request that companies supply the names, test markets, and data for all dissolvables as is done for other tobacco product categories.

Table 2: Tobacco Product Applications as of August, 2011

Products as of 8/ 2011	Number of Submissions
Number of Substantially equivalence submissions (SE) revealed in the	3167
Number of new product submissions (PMTA)	0
Number of modified risk products (MR) received in the months (Oct & Nov) are amendments to previous submissions	7
Dissolvables	?

Table 3: Sample of Industry Document Research on Dissolvables

Title	Date	Company	Author	Bates
Covance Cru Triad 8230249, Switching From Usual Brand Cigarettes to Camel “Snus,” Camel Dissolvable Tobacco “Sticks,” “Strips,” or “Orbs,” Dual Use of Usual Brand Cigarettes and Snus, or Tobacco Abstinence – A Multi-Center Evaluation of Select Modern Smoke-Free Tobacco Products. Protocol CDS0901 (“3S0”).	8/17/2010	RJR	Covance Clinical Research Unit	546203095-3185/yes
RJRT CSD10XX Camel Orbs Smoking Cessation Clinical Trial Synopsis-, A Double-Blind, Placebo-Controlled, Randomized, Parallel Group Design Multi-Center Clinical Trial to Evaluate Smoking Cessation Rates with a Dissolvable Tobacco Product	12/11/2009	RJR	None Listed	556538716-8726/yes
Enterprise Risk Management Review. Alternative Tobacco Products (ATPs)	7/10/2009	RJR	None Listed	556295590-5592/yes
HRRC Proposal. Study to Investigate Use of Tobacco Orbs Compared to Smoking Usual-Brand Cigarettes (HRRC Proposal #0902)	1/13/2009	RJR	Round, EK; Stiles, MF	555663444-3502/yes
Clinical Study Protocol. Assessment of the Effects of Four Dissolvable Tobacco Products Following a 12-Hour Tobacco Abstinence Period	8/26/2010	RJR	Round, EK; Stiles, MF; Chen, P; Borgerding, MF; RJR	546219828-9871/yes
Dissolvable Tobacco Products – A Summary of the Science	8/20/2008	RJR	None Listed	558126731-6733/yes
The Tobacco Cafe: A Dissolvable Tobacco Research Community	2/26/2009	RJR	Bellomy Carrigg	557071373-1399
Public Health Community & Tobacco Control Community, May 17, 2008	5/17/2008	RJR	None Listed	558125768-5823/yes
Camel Sticks/Strips/Orbs do Not Contain Significantly Greater Levels of Nicotine than Other Dissolvable/Smokeless Tobacco Products	11/23/2009	RJR	Howard, DP; Borgerding, MF; Theophilus, S	556631760-1760/yes
Characterization of Tobacco. Labstat International ULC Test Report	10/28/2009	RJR	None Listed	545316627-6647/yes

3. Product Design Analyses:

Limited independent research has been published reporting the chemical components of dissolvable tobacco products. Stepanov et al tested tobacco-specific nitrosamines (TSNAs) in a variety of new tobacco products, including Stonewall and Ariva dissolvable tobacco tablets. Total TSNA levels for Ariva and Stonewall were found to be 0.19 µg/g and 0.28 µg/g respectively, representing the lowest levels of TSNAs among all tobacco products tested. However, nicotine replacement therapy products contained lower levels of TSNAs: patch (0.008 µg/g); gum (0.002 µg/g); lozenge (not detected) (Stepanov, 2006). Further, Rainey and colleagues identified chemical constituents in the previous version of Camel Dissolvables using gas chromatography-mass spectrometry and headspace solid phase micro-extraction. The authors reported the following compounds detected: nicotine, ethyl citrate, palmitic acid, stearic acid, sorbitol, glycerol, xylitol, cinnamaldehyde, coumarin, vanillin, and carvone (Rainey, 2011, in submission).

In research commissioned at HSPH, the most recent iteration of Camel Dissolvables (purchased in Denver, CO) for nicotine, pH, TSNAs, and heavy metals. To our knowledge, no published research has reported constituents in the version of Camel Dissolvables currently available to the public.

3a. Nicotine

Levels of unionized (free) nicotine for Camel Strips Mint, Camel Sticks Mint, and Camel Orbs Mint were found to be 1.91 mg/g, 1.40 mg/g, and 0.84 mg/g, respectively. Multiplying these values by product mass revealed total estimated unionized nicotine for each product: Camel Strips Mint (0.44 mg); Camel Sticks Mint (0.64 mg); Camel Orbs Mint (0.19 mg/g). (Table 3).

Table 4. Measured Nicotine Levels in Camel Dissolvables

Product	Mass (g)	pH	Nicotine (mg/g)	Unionized Nicotine# (mg/g)	Unionized Nicotine (%)	Unionized Nicotine/ Dissolvable (mg)
Camel Strips Mint	0.23	8.03	3.77	1.91	50.66	0.44
Camel Sticks Mint	0.46	7.67	4.53	1.40	30.91	0.64
Camel Orbs Mint	0.23	7.52	3.48	0.84	24.14	0.19
General Snus Original		7.77	14.76	5.31	35.99	
Nicorette Lozenge Original*	1.21	8.97	3.14	2.82	89.91	3.41
Marlboro Sticks Cool Mint†						

*3 mg nicotine, testing currently underway

Number calculated by entering the measured values for pH and nicotine into the Henderson-Hasselbalch equation, while using a pKa value of 8.02

It is important to note that the nicotine content may not represent the quantity of nicotine absorbed into the blood or the amount that reaches the brain. Use behavior (placement in mouth, length of use, swallowing, and number of dissolvables used) will influence the amount of nicotine delivered. Further, information on the topography of dissolvables is currently not available, and more research is needed on the topography, dual use of this product, and nicotine exposure to understand the public health impact.

3b. Tobacco Specific Nitrosamines (TSNAs)

TSNAs are carcinogenic compounds found in tobacco products. Table 4 provides data on the levels of TSNAs detected in Camel Dissolvables. Total TSNA levels were found to be 1352 ng/g, 240 ng/g, and 1303 ng/g for Camel Strips Mint, Camel Sticks Mint, and Camel Orbs Mint respectively. None of the products contained NAB, while NNK (a potent carcinogen) was the highest detected TSNA for Camel Strips Mint and Camel Orbs Mint. NNK was not quantifiable for Camel Sticks Mint. These levels detected are lower than levels measured in popular moist snuff brands (Total TSNAs: Copenhagen Long Cut Original, 11,635 ng/g; Skoal Long Cut Wintergreen, 12,222 ng/g).

Table 5 TSNA levels in Camel Dissolvables

Product	NNN (ng/g)	NAT (ng/g)	NAB (ng/g)	NNK (ng/g)	Total TSNAs (ng/g)
Camel Strips Mint	360	348	NQ	644	1352
Camel Sticks Mint	240	NQ	NQ	NQ	240
Camel Orbs Mint	293	312	NQ	698	1303
General Snus Original	783	502	NQ	NQ	1285
Nicorette Lozenge Original*	BDL	BDL	BDL	BDL	N/A
Marlboro Sticks Cool Mint†					

*3 mg nicotine

† Testing currently underway

NQ= Not quantifiable

3c. Heavy Metals

Toxic heavy metals are found in tobacco products and may contribute to cancer and non-cancer (e.g. heart disease) outcomes. Cadmium, lead, chromium, nickel, arsenic, and mercury were detected in all products, while no products contained quantifiable levels of selenium. Chromium levels were highest among all metals detected for all products followed by nickel. Levels of mercury were lowest for all products among quantifiable metals (Table 5).

Table 6 Measured Levels of Metals in Camel Dissolvables

Product	Cadmium (ng/g)	Lead (ng/g)	Chromium (ng/g)	Nickel (ng/g)	Arsenic (ng/g)	Selenium (ng/g)	Mercury (ng/g)
Camel Strips Mint	341	226	1464	568	171	BDL	12.4
Camel Sticks Mint	259	195	963	533	174	BDL	11.1
Camel Orbs Mint	346	139	715	554	171	NQ	14.4
General Snus Original	390	160	500	769	98.1	98.4	18
Nicorette Lozenge Original*	BDL	NQ	81.9	NQ	80.5	BDL	NQ
Marlboro Sticks Cool Mint†							

*3 mg nicotine

† Testing currently underway

Metal Contaminant Acceptance Levels

Heavy metals are known to cause health effects at various stages of life, including cancer, and particular susceptibility to neurobiological effects in the fetus and during developmental stages of life. A number of heavy metal constituents have been found in smokeless tobacco and tobacco in all forms. These include arsenic (As), cadmium (Cd), chromium (Cr), cobalt (Co), lead (Pb), mercury (Hg), and nickel (Ni), and others. Primary sources for regulatory values and guidelines include the U.S. Food and Drug Administration (FDA), U.S. Environmental Protection Agency (USEPA), Joint Food and Agricultural Organization / World Health Organization Expert Committee on Food Additives (JECFA), U.S. Agency for Toxic Substances and Disease Registry (ATSDR), California's Safe Drinking Water and Toxic Enforcement Act of 1986, and American National Standards Institute (ANSI) National Sanitation Foundation (NSF). The basis of the calculations for the acceptable or tolerable levels of the metals in the finished product follows a mathematical model in which an acceptable or tolerable daily intake in mg/kg body weight is multiplied by the average mass of an adult (60 or 65 kg for women, and 70 or 75 kg for men).

Arsenic

The NSF recommends an acceptable daily intake of 0.01 mg per day in finished products containing arsenic based on JECFA provisional maximum tolerable weekly intake of 0.015 mg per kg body weight. The USEPA IRIS toxicological review of arsenic determined an oral RfD of 0.0003 mg per kg of body weight per day based on a NOAEL of 0.0008 mg per kg body weight per day in humans and an uncertainty factor of three. The FDA regulates the concentration of arsenic in bottled water and allows a maximum level of 10 µg / L. (21 CFR

165.110(b)(4)(iii)(A)). California's Safe Drinking Water and Toxic Enforcement Act of 1986 lists arsenic as a carcinogen with a no-significant risk level of 0.06 µg per day for routes of exposure other than inhalation.

Cadmium

The NSF recommends an acceptable daily intake of 0.06 mg cadmium per day in finished products based on JECFA provisional maximum tolerable weekly intake of 0.007 mg per kg body weight. The USEPA set a reference dose of 0.005 mg per kg body weight per day for food and water based on a NOAEL of 0.01 mg per kg body weight per day and an uncertainty factor of 10. The FDA set a level of 0.005 mg per L cadmium allowed in bottle water (21 CFR 103.35) and 0.05 ppm for amount of cadmium allowable in zinc methionine sulfate tablets. The ATSDR set a minimum risk level for cadmium at 0.0002 mg per kg body weight per day.

Chromium

The NSF recommends an acceptable daily intake of 0.18 mg chromium based on the EPA oral reference dose (RfD) of 0.003 mg per kg body weight per day. The USEPA set an RfD of 0.003 mg per kg body weight per day for chromium. The FDA set a reference daily intake for chromium of 120 µg per day based on adult exposures and found inadequate data appropriate for use in determining recommended chromium exposures for children. ATSDR draft toxicological profile for chromium derives an oral minimum risk level (MRL) of 0.005 mg chromium (VI) per kg body weight per day for intermediate exposure 0.001 mg chromium (VI) per kg body weight per day for chronic exposure.

Lead

The NSF recommends a tolerable daily intake of 0.24 mg lead based on JECFA provisional maximum tolerable weekly intake of 0.025 mg per kg body weight. The USEPA has considered deriving an oral RfD for inorganic to be in appropriate due to the harmful effects occurring at blood levels for which a threshold could not be established. The USEPA set an action level of 0.015 mg per L in the 90th percentile of first-draw tap water samples. The FDA derived provisional tolerable intake levels of lead at 25 µg per day for pregnant women and 6 µg per day for infants.

Mercury

The NSF recommends an acceptable daily intake of inorganic mercury of 0.02 mg based on the USEPA RfD of 0.0003 mg per kg body weight per day.

Cobalt

The ATSDR derived an MRL of 0.01 mg cobalt/kg-day for intermediate-duration oral exposure.

Based on the information supplied above and the heavy metal concentrations in dissolvable products, much more research needs to be done on how dissolvables levels match against those established by scientific agencies.

4. Physical Health Effects

4a. Pancreatic and Oral Cancer

The International Agency on Cancer Research in 2008 concluded that smokeless tobacco causes oral and pancreatic cancer regardless of type.

International Agency for Research on Cancer. Monograph 89: Smokeless Tobacco and Some Tobacco specific N-Nitrosamines, 2007.

<http://monographs.iarc.fr/ENG/Monographs/vol89/index.php>; summarized in:

Cogliano V, Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F. Smokeless tobacco and tobacco-related nitrosamines. *Lancet Oncol.* 2004 Dec;5(12):708.

Many types of smokeless tobacco are marketed for oral or nasal use, and all contain different amounts of nicotine and nitrosamines. Overall, there is sufficient evidence that smokeless tobacco causes oral cancer and pancreatic cancer in humans, and sufficient evidence of carcinogenicity from animal studies. Tobacco-specific nitrosamines such as N'-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosoanatabine (NAT), and iST-nitrosoanabasine (NAB), form by the nitrosation of nicotine and other tobacco alkaloids. Substantial quantities form during the curing and processing of tobacco. Our Center's Tobacco Control Working Group concluded that exposure to NNN and NNK is "carcinogenic to humans" on the basis of sufficient evidence from animals and strong mechanistic evidence in exposed humans.

4b. Fetal and neonatal effects: research on Swedish snus which is similar to dissolvables in design, shows a high risk to adverse fetal health

Relationship of Maternal Snuff Use and Cigarette Smoking With Neonatal Apnea. Gunnerbeck A, Wikström AK, Bonamy AK, Wickström R, Cnattingius S. *Pediatrics*. 2011 Aug 28. [Epub ahead of print]

Compared with infants of non-tobacco users, infants with prenatal exposure to snuff were at an increased risk of apnea even after adjustment for differences in gestational age (odds ratio: 1.96 [95% confidence interval: [1.30-2.96])). Smoking was associated with increased risk of apnea before, but not after, adjusting for gestational age.

Conclusions: Snuff use during pregnancy is associated with a higher risk of neonatal apnea than smoking. Maternal use of snuff or nicotine-replacement therapy cannot be regarded as an alternative to smoking during pregnancy.

Effect of Swedish snuff (snus) on preterm birth. Wikström AK, Cnattingius S, Galanti MR, Kieler H, Stephansson O. BJOG. 2010 Jul;117(8):1005-10

Compared with non-tobacco users, snuff users had increased risks of both very (adjusted OR 1.38; 95% CI 1.04-1.83) and moderately (adjusted OR 1.25; 95% CI 1.12-1.40) preterm birth. Compared with non-tobacco users, light smokers had increased risks of both very (adjusted OR 1.60; 95% CI 1.42-1.81) and moderately (adjusted OR: 1.18; 95% CI: 1.12-1.24) preterm birth, and heavy smokers had even higher risks. Among smokers, but not among snuff users, the risk was more pronounced for spontaneous than induced preterm birth.

Conclusions: The use of Swedish snuff was associated with increased risks of very and moderately preterm birth with both spontaneous and induced onsets. Swedish snuff is not a safe alternative to cigarette smoking during pregnancy.

Maternal smokeless tobacco use in Alaska Native women and singleton infant birth size. England LJ, Kim SY, Shapiro-Mendoza CK, Wilson HG, Kendrick JS, Satten GA, Lewis CA, Whittern P, Tucker MJ, Callaghan WM. Acta Obstet Gynecol Scand. 2011 Sep 9. doi: 10.1111/j.1600-0412.2011.01273.x. [Epub ahead of print]

After adjustment for gestational age and other potential confounders, the mean birthweight of infants of smokeless tobacco users was reduced by 78g compared with that of infants of non-users ($p=0.18$), and by 331g in infants of smokers ($p<0.01$). No association was found between maternal smokeless tobacco use and infant length or infant head circumference.

Conclusions: We found a modest but non-significant reduction in the birthweight of infants of smokeless tobacco users compared with infants of tobacco non-users. Because smokeless tobacco contains many toxic compounds that could affect other pregnancy outcomes, results of this study should not be construed to mean that smokeless tobacco use is safe during pregnancy.

Effect of Swedish snuff (snus) on preterm birth. Wikström AK, Cnattingius S, Galanti MR, Kieler H, Stephansson O. BJOG. 2010 Jul;117(8):1005-10.

Results: Compared with non-tobacco users, snuff users had increased risks of both very (adjusted OR 1.38; 95% CI 1.04-1.83) and moderately (adjusted OR 1.25; 95% CI 1.12-1.40) preterm birth. Compared with non-tobacco users, light smokers had increased risks of both very (adjusted OR 1.60; 95% CI 1.42-1.81) and moderately (adjusted OR: 1.18; 95% CI: 1.12-1.24) preterm birth, and heavy smokers had even higher risks. Among smokers, but not among snuff users, the risk was more pronounced for spontaneous than induced preterm birth.

Conclusions: The use of Swedish snuff was associated with increased risks of very and moderately preterm birth with both spontaneous and induced onsets. Swedish snuff is not a safe alternative to cigarette smoking during pregnancy.

4c. Pregnancy

Compared with non-tobacco users, women who used snuff in early pregnancy had an adjusted odds ratio (OR) for pre-eclampsia of 1.11 (95% CI: 0.97 to 1.28). The corresponding ORs for light and heavy smokers were 0.66 (95% CI: 0.61 to 0.71) and 0.51 (95% CI: 0.44 to 0.58) respectively, with ORs lower for term than preterm pre-eclampsia. Compared with non-tobacco users, women who smoked in early pregnancy but had quit smoking before late pregnancy (weeks 30 to 32) had an adjusted OR for term pre-eclampsia of 0.94 (95% CI: 0.83 to 1.08). The corresponding OR for women who did not use tobacco in early pregnancy but had started to smoke before late pregnancy was 0.65 (95% CI: 0.50 to 0.85). We conclude that tobacco combustion products rather than nicotine are the probable protective ingredients against pre-eclampsia in cigarette smoke.

Non-cigarette tobacco use among women and adverse pregnancy outcomes. England LJ, Kim SY, Tomar SL, Ray CS, Gupta PC, Eissenberg T, Cnattingius S, Bernert JT, Tita AT, Winn DM, Djordjevic MV, Lambe M, Stamilio D, Chipato T, Tolosa JE. Acta Obstet Gynecol Scand. 2010;89(4):454-64.

Although cigarette smoking remains the most prevalent form of tobacco use in girls and in women of reproductive age globally, use of non-cigarette forms of tobacco is prevalent or gaining in popularity in many parts of the world, especially in low- and middle-income countries. Sparse but growing evidence suggests that the use of some non-cigarette tobacco products during pregnancy increases the risk of adverse pregnancy outcomes.

4d. Cardiovascular Disease:

Recent research from Sweden raises serious concerns about use of snus and possibly dissolvables given their similarities to cardiovascular disease

Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. Bolinder G, Alfredsson L, Englund A, de Faire U. Am J Public Health. 1994 Mar; 84(3):399-404.

The study population comprised 6,297 smokeless tobacco users, 14,983 smokers of fewer than 15 cigarettes per day, 13,518 smokers of 15 or more cigarettes per day, 17,437 ex-smokers, 50,255 other tobacco users, and 32,546 nonusers. Results: The age-adjusted relative risk of dying from cardiovascular disease was 1.4 for smokeless tobacco users and 1.9 for smokers of 15 or more cigarettes per day compared with nonusers. Among men aged 35 through 54 years at the start of follow-up, the relative risk was 2.1 for smokeless tobacco users and 3.2 for smokers. When data were adjusted for body mass index, blood pressure, and history of heart symptoms, the results were essentially unchanged. Cancer mortality was not raised in smokeless tobacco users. Both smokeless tobacco users and smokers face a higher risk of dying from cardiovascular disease than nonusers. Although the risk is lower for smokeless tobacco users than for smokers, the excess risk gives cause for preventive actions. Smokeless tobacco (snus) and risk of heart failure: results from two Swedish cohorts.

Arefalk G, Hergens MP, Ingelsson E, Arnlöv J, Michaëlsson K, Lind L, Ye W, Nyrén O, Lambe M, Sundström J. Eur J Cardiovasc Prev Rehabil. 2011 Aug 9. [Epub ahead of print]

Two independent Swedish prospective cohorts provided valuable information on the risk of cardiovascular disease. The Uppsala Longitudinal Study of Adult Men (ULSAM) involved a community-based sample of 1076 elderly men and the Construction Workers Cohort Study (CWC) involved a sample of 118,425 never-smoking male construction workers. In ULSAM, 95 men were hospitalized for heart failure during a median follow up of 8.9 years. In a model adjusted for established risk factors including past and present smoking exposure, current snus use was associated with a higher risk of heart failure [hazard ratio (HR) 2.08, 95% confidence interval (CI) 1.03-4.22] relative to non-use. Snus use was particularly associated with risk of non-ischemic heart failure (HR 2.55, 95% CI 1.12-5.82). In CWC, 545 men were hospitalized for heart failure during a median follow up of 18 years. In multivariable-adjusted models, current snus use was moderately associated with a higher risk of heart failure (HR 1.28, 95% CI 1.00-1.64) and non-ischemic heart failure (HR 1.28, 95% CI 0.97-1.68) relative to never tobacco use. Data from two independent cohorts suggest that use of snus may be associated with a higher risk of heart failure.

Risk of incident cardiovascular disease among users of smokeless tobacco in the Atherosclerosis Risk in Communities (ARIC) study. Yatsuya H, Folsom AR; ARIC Investigators. Am J Epidemiol. 2010 Sep 1; 172(5):600-5.

The authors examined whether current use of smokeless tobacco was associated with increased incidence of cardiovascular disease (CVD) in 14,498 men and women aged 45-64 years at baseline (1987-1989) in the Atherosclerosis Risk in Communities (ARIC) Study. There were 2,572 incident CVD events (myocardial infarction, coronary revascularization, coronary death, or stroke) during a median of 16.7 years of follow-up (maximum = 19.1 years). Current use of smokeless tobacco at baseline was associated with 1.27-fold greater CVD incidence (95% confidence interval: 1.06, 1.52) than was nonuse, independently of demographic, socioeconomic, and lifestyle and other tobacco-related variables. Past use of smokeless tobacco was not associated with CVD incidence.

In conclusion, current use of smokeless tobacco was associated with increased risk of CVD incidence in ARIC cigarette nonsmokers. Current users of smokeless tobacco should be informed of its harm and advised to quit the practice. Current cigarette smokers should also be given sufficient information on safe, therapeutic methods of quitting which do not include switching to smokeless tobacco.

Smokeless tobacco and the risk of stroke. Hergens MP, Lambe M, Pershagen G, Terent A, Ye W. Epidemiology. 2008 Nov;19(6):794-9.

Information on tobacco use was collected by questionnaire among Swedish construction workers attending health check-ups between 1978 and 1993. In total, 118,465 never-smoking men without a history of stroke were followed through 2003. They used the Inpatient Register and Causes of Death Register to identify subsequent morbidity and mortality from stroke and its

subtypes (ischemic, hemorrhagic, and unspecified stroke). Almost 30% of the nonsmoking men had ever used snuff. Overall, 3248 cases of stroke were identified during follow-up. Compared with nonusers of tobacco, the multivariable-adjusted relative risks for ever-users of snuff were 1.02 (95% confidence interval; 0.92-1.13) for all cases and 1.27 (0.92-1.76) for fatal cases. Further analyses on subtypes of stroke revealed an increased risk of fatal ischemic stroke associated with current snuff use (1.72; 1.06-2.78), whereas no increased risk was noted for hemorrhagic stroke. Snuff use may elevate the risk of fatal stroke, and particularly of fatal ischemic stroke.

Risk of hypertension amongst Swedish male snuff users: a prospective study. Hergens MP, Lambe M, Pershagen G, Ye W. J Intern Med. 2008 Aug;264(2):187-94.

This examined the risk of hypertension in relation to long-term use of snuff based on longitudinal data. Repeated health check-ups were offered to all employees in the Swedish construction industry between 1978 and 1993. Blood pressure was measured at the health check-up and information on tobacco use and other risk factors was collected through questionnaires. In total, 120 930 never smoking men with information on blood pressure and snuff use at baseline were included. The association of high blood pressure and snuff use at baseline was estimated by logistic regression. Further, 42 055 men were identified as normotensive at baseline and had at least one subsequent health check-up. Through repeated blood pressure measurements and linkage to the Swedish National Inpatient Register, information on hypertension was obtained. Almost 30% of all men had used snuff. The adjusted odds ratio of high blood pressure amongst snuff users at baseline was 1.23 (95% CI 1.15-1.33) compared to never snuff users. The relative risk of high blood pressure during follow-up was 1.39 (95% CI 1.08-1.79) amongst snuff users and 1.36 (95% CI 1.07-1.72) for hypertension as recorded in the Inpatient Register. Conclusion: Use of Swedish moist snuff appears to be associated with a moderately increased risk of hypertension.

Long-term use of Swedish moist snuff and the risk of myocardial infarction amongst men. Hergens MP, Alfredsson L, Bolinder G, Lambe M, Pershagen G, Ye W. J Intern Med. 2007 Sep;262(3):351-9.

This study examined whether long-term use of snuff affects the risk of myocardial infarction. Between 1978 and 1993 all construction workers in Sweden were offered repeated health check-ups by the Swedish Construction Industry's Organization for Working Environment Safety and Health. A cohort was created with information on tobacco use and other risk factors, collected through questionnaires.

Setting: In total, 118,395 nonsmoking men without a history of myocardial infarction were followed through 2004. Information on myocardial infarction morbidity and mortality was obtained from national registers. Almost 30% of the men had used snuff. In total, 118,395 nonsmoking men without a history of myocardial infarction were followed through 2004. The multivariable-adjusted relative risks for ever snuff users were 0.91 (95% confidence interval, 0.81-1.02) for nonfatal cases and 1.28 (95% confidence interval, 1.06-1.55) for fatal cases. Heavy users (≥ 50 g/day(-1)) had a relative risk of fatal myocardial infarction of 1.96 (95% confidence interval, 1.08-3.58). Snuff use increased the probability of mortality from

cardiovascular disease amongst nonfatal myocardial infarction patients. The results indicate that snuff use is associated with an increased risk of fatal myocardial infarction.

Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. Boffetta P, Straif K. BMJ. 2009 Aug 18;339:b3060. doi: 10.1136/bmj.b3060.

Eleven studies, mainly in men, were included. Eight risk estimates were available for fatal myocardial infarction: the relative risk for ever use of smokeless tobacco products was 1.13 (95% confidence 1.06 to 1.21) and the excess risk was restricted to current users. The relative risk of fatal stroke, on the basis of five risk estimates, was 1.40 (1.28 to 1.54). The studies from both the United States and Sweden showed an increased risk of death from myocardial infarction and stroke. The inclusion of non-fatal myocardial infarction and non-fatal stroke lowered the summary risk estimates. Data on dose-response were limited, but did not suggest a strong relation between risk of dying from either disease and frequency or duration of use of smokeless tobacco products. An association was detected between use of smokeless tobacco products and risk of fatal myocardial infarction and stroke, which does not seem to be explained by chance.

4e. Child Poisonings

Unintentional child poisonings through ingestion of conventional and novel tobacco products. Connolly GN, Richter P, Aleguas A Jr., Pechacek TF, Stanfill SB, Alpert HR. Pediatrics. 2010 May; 125(5):896-9.

This study examined child poisonings resulting from ingestion of tobacco products throughout the nation and assessed the potential toxicity of novel smokeless tobacco products, which are of concern given their discreet form, candy-like appearance, and added flavorings that may be attractive to young children. Data representing all single-substance, accidental poisonings resulting from ingestion of tobacco products by children <6 years of age, reported to poison control centers, were examined. Age association with ingestion of smokeless tobacco versus other tobacco products was tested through logistic regression. Total nicotine content, pH, and un-ionized nicotine level were determined, and the latter was compared with values for moist snuff and cigarettes.

Results: A total of 13,705 tobacco product ingestion cases were reported, >70% of which involved infants <1 year of age. Smokeless tobacco products were the second most common tobacco products ingested by children after cigarettes, and represented an increasing proportion of tobacco ingestions with each year of age from 0 to 5 years (odds ratio: 1.94 [95% confidence interval: 1.86-2.03]). A novel, dissolvable, smokeless tobacco product with discreet form, candy-like appearance, and added flavorings was found to contain an average of 0.83 mg of nicotine per pellet with an average pH of 7.9, resulting in an average of 42% of the nicotine in the un-ionized form. In light of the novelty and potential harm of dissolvable nicotine products, public health authorities are advised to study these products to determine the appropriate regulatory approach.

4f. Overall Mortality among Smokers who Switched to Spit tobacco

Tobacco-related disease mortality among men who switched from cigarettes to spit tobacco. Henley SJ, Connell CJ, Richter P, Husten C, Pechacek T, Calle EE, Thun MJ. Tob Control. 2007 Feb;16(1):22-8.

A cohort of 116,395 men was identified as switchers (n = 4443) or cigarette smokers who quit using tobacco entirely (n = 111,952) when enrolled in the ongoing US American Cancer Society Cancer Prevention Study II. From 1982 to 31 December 2002, 44,374 of these men died. The mortality hazard ratios (HR) of tobacco-related diseases, including lung cancer, coronary heart disease, stroke and chronic obstructive pulmonary disease, were estimated using Cox proportional hazards regression modeling adjusted for age and other demographic variables, as well as variables associated with smoking history, including number of years smoked, number of cigarettes smoked and age at quitting.

Results: After 20 years of follow-up, switchers had a higher rate of death from any cause than those who quit using tobacco entirely (HR 1.08, 95% confidence interval (CI) 1.01 to 1.15), lung cancer (HR 1.46, 95% CI 1.24 to 1.73), coronary heart disease (HR 1.13, 95% CI 1.00 to 1.29), and stroke (HR 1.24, 95% CI 1.01 to 1.53).

Conclusion: The risks of dying from major tobacco-related diseases were higher among former cigarette smokers who switched to spit tobacco after they stopped smoking than among those who quit using tobacco entirely.

4g. Scientific Standards for Expressing Toxic Risk for Dissolvables

Applying toxicological risk assessment principles to constituents of smokeless tobacco products: implications for product regulation, Olalekan A. Ayo-Yusuf and Gregory N. Connolly, Tobacco Control 2011 20: 5357 originally published on line October 5, 2010. (doi: 10.1136/tc.2010.037135)

This study investigated select STP constituents potentially associated with significant cancer risk by applying a known toxicological risk assessment framework. Cancer risk estimates were obtained for selected constituents of STPs. They also made a medicinal nicotine gum formulation with comparable toxicity information and collected median concentration data on the GothiaTek analytes. The calculated cancer risk was considered 'unacceptable' if it exceeded the US Environmental Protection Agency's (USEPA's) benchmark of an 'acceptable' cancer risk of 10E₋₆.

The cancer risk estimates derived from daily use of 10 g of STPs were 8,000 times greater than the industry-set GothiaTek limit standard (generally considered acceptable by the USEPA). Except for the medicinal nicotine tested, all the STP types, including the relatively lower tobacco specific nitrosamine (TSNA)-containing snus, were found to carry an unacceptable cancer risk. The calculated cancer risks associated with the snus and the US moist snuff products were, respectively, at least 1000 times and 6000 times greater than the minimum acceptable level.

TSNA and cadmium are associated with the largest estimated cancer risks for all the STPs evaluated.

This study's findings provide an empirical risk assessment that could guide STP regulation using an existing toxicological assessment framework. The study findings question the scientific rationale of the industry set standards.

5. Abuse Liability

Currently Harvard School of Public Health Research

Research at HSPH has examined the abuse liability of new MRTPs. Measuring the abuse liability of products allows an understanding of the likelihood of future interest and adoption of a dissolvable and products by consumer. The information provides a basis for understanding the potential abuse liability of dissolvable products.

Research at Harvard School of Public Health has focused on understanding the abuse liability of modified risk tobacco products. Abuse liability may be defined as the potential for a drug or product to promote dependence in a user. Dependence involves both initiation in a non-user, as well as maintenance escalation to established user relapse following quitting. Abuse liability of a tobacco product accrues through interplay among multiple factors including pharmacological effects of nicotine, social factors, chemosensory perceptions, interceptive cues for use and dosing, psychological and other factors. External social stimuli include price, marketing, access, packaging and others.

A product which delivers a low-moderate amount of nicotine may have higher abuse liability for a non-tobacco user as it will allow initiation without the adverse effects associated with high nicotine dosing. Likewise, attractive chemosensory effects, high social acceptability, low perceptions of risk, low cost, flavors, appearance and easy access will contribute to high abuse liability among non-tobacco using youth.

Conversely, a product with low nicotine delivery may generate low abuse liability among established tobacco users. However, social factors, such the enhanced opportunity to use dissolvables indoors, low cost, and low risk perceptions may be sufficient to maintain product appeal among smokers. The low level of nicotine delivery, and thus lowered abuse liability compared with a conventional cigarette, may hinder complete switching from a cigarette to a product such as a dissolvable. Thus dual use of dissolvables with cigarettes is a possible response. Many advertisements for American snus products promote dual use, possibly countering social factors that deter smoking.



Figure 2: Example of smokeless – cigarette product dual use marketing

5a. Consumer Response Research

Perceptions of Product Messaging

Consumer perception data on dissolvables are not currently available. However, a web-based survey (N=150) conducted by Harvard School of Public Health on a snus product – Camel Snus – may provide indicative evidence on consumer responses to dissolvables. When shown Camel Snus marketing materials, regular smokers interpreted the snus products as a modern, exciting product which was easy to understand. The main message take away from the advertisements was ‘to use when you can’t smoke’ (50%). The Camel Snus packaging was found to be appealing to 53% of the sample, while the package color was somewhat or extremely appealing to 65% of respondents. Only 19% were interested in trying the product based on its name.

The most appealing aspect of snus was that it was ‘smokeless and spitless’ (46%) and ‘for use in situations when I can’t smoke’ (28%). Most respondents believed Camel snus would be appealing to young adults (62%) and busy people (52%).

Nearly half of respondents (49%) expected Camel snus to provide equal or more satisfaction than their usual brand of cigarettes. Men were 3.3 times more likely (OR=3.29 95% CI 1.44, 7.52) than females to expect equal or more satisfaction from Camel snus (logistic regression controlling for age, hsi and education level – all $p > .05$). Thirteen percent (13%) of respondents

intended to purchase and try Camel snus within the next month. Likelihood of complete switching to Camel snus was relatively low with only 6% reporting that they would probably or definitely switch. However, likelihood of dual use was higher with 13% reporting that they would probably or definitely use snus regularly in addition to cigarettes.

Response to Product Use

Independent research has examined the responses to dissolvables product use. Kotlyar and colleagues examined responses to dissolvable tobacco lozenges, Ariva, Stonewall and Revel. These products were produced only low plasma nicotine levels, compared with Copenhagen snuff and the nicotine replacement product, Commit. Ariva was less effective than the control products at reducing urge to smoke (Kotlyar, et al. 2007). Other investigators have demonstrated similar low nicotine levels from tobacco lozenges, as well as poor suppression of nicotine abstinence symptoms and low consumer acceptability (Blank & Eissenberg, 2010; Cobb et al. 2010). Consumption of greater quantities of Ariva lozenges may produce higher nicotine levels, but are not well tolerated by consumers (Mendoza-Baumgart, 2007).

Sampling by consumers of different modalities of smokeless tobacco products may be important in determining appeal of those products. Hatsukami and colleagues demonstrated that smokers showed low preference for General Snus and equal preferences for Camel Snus, Marlboro Snus, Ariva and Stonewall after two weeks of trial. Further research is needed on what product design features of smokeless tobacco products consumers promote appeal among current smokers, and those intending to quit. Nicotine dosing, additives that provide flavor and other desirable chemosensory effects, ease and convenience of use and brand image may be factors that enhance acceptability among consumers.

Evidence to date suggests that low nicotine levels produced by nicotine lozenges fail to suppress smoking urges and have low acceptability compared with a conventional cigarette. This provides preliminary evidence for low abuse liability of dissolvables products, and raises concerns that dissolvables may not provide a viable alternative for smokers. They may instead be used dually. Further research on dissolvables products is needed to assess key abuse liability measures compared with conventional cigarette and other novel smokeless products. Assessment should include: capacity to reduce urges and withdrawal among regular smokers, effect and liking ratings, and risk perceptions. Clinical trials are needed to understand the likely pattern of dissolvables use in a natural setting, including dual use with cigarettes, as well as influence of dissolvables use on nicotine dependence, cigarette consumption, and cotinine levels.

5b. Smokeless Tobacco as “Starter” Product for Youth Initiation

**The marketing of nicotine addiction by one oral snuff manufacturer
Gregory N. Connolly - Tobacco Control 1995; 4: 73-79.**

This article reviews internal industry documents offered into evidence in a 1986 Oklahoma court case, tobacco and advertising industry trade literature, and advertising and promotional material showing how one snuff manufacturer markets nicotine dependence to young people through the design and marketing of low nicotine snuff products.

5c. Internal Tobacco Industry Documents and Combined Tobacco Use

Developing smokeless tobacco products for smokers: an examination of tobacco industry documents - Carrie M. Carpenter, Gregory N. Connolly, Olalekan A. Ayo-Yusuf, Geoffrey Ferris Wayne – Tobacco Control 2009; 18: 54-59.

This study analyzed internal tobacco industry documents to describe research related to the smokeless tobacco market. Relevant documents included those detailing the development and targeting of SLT products with a particular emphasis on moist snuff. Cigarette and SLT manufacturers recognized that shifting demographics of SLT users, as well as indoor smoking restrictions, health concerns and reduced social acceptability of smoking, could impact the growth of the SLT market. Manufacturers developed new SLT products to target cigarette smokers, promoting dual cigarette and SLT use.

Heavy marketing of new SLT products may encourage dual use, resulting in unknown public health effects. SLT products have been designed to augment cigarette use and offset regulatory strategies such as clean indoor air laws. In the United States, the SLT strategy may provide cigarette companies with a diversified range of products under the prospect of federal regulation. These products may pose significant challenges to efforts by federal agencies to reduce harm caused by tobacco use.

5d. Smokeless tobacco has not been shown as an effective method for quitting smoking.

**Scientific Committee on Emerging and Newly Identified Health Risks
SCENIHR, Health Effects of Smokeless Tobacco Products
The SCENIHR adopted this opinion at the 22nd plenary on 6 February 2008**

The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) was asked to evaluate the health effects of smokeless tobacco products (STP) and examined published studies on smokeless tobacco as a method for cessation.

5e. Smokeless tobacco use increases the risk of young people who start with smokeless tobacco to become smokers and adults are far more likely to switch from smokeless tobacco to cigarette than from cigarettes to smokeless.

Patterns of dual use of cigarettes and smokeless tobacco among U.S. males: findings from national survey, Scott L. Tomar, Hillel R. Alpert and Gregory N. Connolly, Tobacco Control, December 11, 2009 (doi: 10.1136/tc.2009.031070)

This study examined patterns of concurrent use of smokeless tobacco (ST) and cigarettes among young people and adults in the USA immediately prior to cigarette companies' control of the nation's ST market. Data were drawn from four U.S. nationally representative surveys. Stratified analyses applied sampling weights and accounted for the complex sample designs.

Cigarette smoking was substantially more prevalent among young males who used ST than among those who did not. Among adult males, those who smoked daily were less likely than others to have used snuff every day. Men who used moist snuff daily had the lowest prevalence of daily smoking, but the prevalence of daily smoking was relatively high among men who used moist snuff less than daily. Unsuccessful past-year attempts by daily smokers to quit smoking were more prevalent among non-daily snuff users (41.2%) than among those who had never used snuff (29.6%).

Although dual daily use of ST and cigarettes is relatively uncommon in the USA, concurrent ST use is more common among adolescent and young adult male smokers than among more mature tobacco users. Among adult males, daily smoking predominates and non-daily ST use is very strongly associated with current smoking. Adult male smokers who also use ST daily tend to have relatively high levels of serum cotinine and high prevalence of a major indicator for tobacco dependence.

6. Summary

There is an absence of scientific data proving that dissolvables will reduce harm on an individual or a population level. Conversely, there is ample evidence suggesting increased individual and population health risks. Based on the likely low abuse liability, dissolvables are unlikely to provide an acceptable replacement for cigarettes in smokers not currently seeking to quit. Thus, initiation and dual use of cigarettes and dissolvables could be an outcome. Use of cigarettes at any level adversely affects health outcomes. Moreover, the potential for dissolvables to promote initiation among youth and delay cessation among current smokers may undermine the steady decline in smoking prevalence observed over the past decades, as well as an initiative to halt sales and conduct research is in keeping with the legal mandate of FSTPC. The adverse health effects of Swedish Snus on the fetus, the risk of child poisoning, and increased risk of cardiovascular disease represent major concerns that must be considered before allowing its sale.

The FDA and TPSAC should require dissolvable manufacturers to conduct a thorough scientific examination of the individual and population effects before their sale is allowed based on FDA protocol.

We recommend that the following steps be taken:

1. Require research on dissolvables to prevent youth initiation, combined use, and relapse among former tobacco users. This may be done by conducting research on inert additives or fixed nicotine levels that make the product unacceptable to youth and former tobacco users;
2. Conduct research on limits on toxins based on scientific methods, such as those by the Food and Drug Administration or other science entities for toxins including nitrosamines, heavy metals, and poly-aromatic hydrocarbons;
3. Prohibit the use of all flavorants including wintergreen in smokeless tobacco products and adjustment of pH through addition of pH modifiers;
4. Conduct research on heavy metals and adverse health effects;

5. Require research on packaging to prevent youth under 18 of age from opening the package (based on standards set by the Consumer Products Safety Commission or others);
6. Ban the future use of dissolvables by pregnant women;
7. Require tobacco companies to conduct IRB-approved clinical trials to protect youth or former smokers from continuing to smoke (as is done with drug companies);
8. Prevent cigarette manufactures from selling dissolvable tobacco products based on conflicts of interest until they enter into a written consent with the FDA stipulating that they will end the sale of cigarettes within three years.